Posttherapy topographical nodal status, ypN-site, predicts survival of patients who received neoadjuvant chemotherapy followed by curative surgical resection for non-type 4 locally advanced gastric cancer: supplementary analysis of JCOG1004-A

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Abstract

Background Perioperative treatment is an accepted standard approach for treating locally advanced gastric cancer (LAGC). Histopathological tumor regression with < 10% residual tumor is a globally accepted prognosticator in LAGC patients who received neoadjuvant chemotherapy (NAC) and curative surgery. However, despite a response of the primary tumor, a significant percentage of patients dies from recurrence and identification of those at risk for relapse remains challenging. We re-estimated the value of histopathological tumor regression as a prognosticator alongside other factors, especially posttherapy topographical nodal status, ypN-site.

Patients and methods Individual patient data including clinicopathological variables were used from the four JCOG trials investigating NAC (JCOG0001, JCOG0002, JCOG0210, JCOG0405) for analyzing prognosticators in patients with curative surgery excluding those with type 4 AGC by univariable and multivariable Cox regression analyses.

Results Among 85 patients, 5-year overall survival (OS) was 46.0% [95% confidence interval (CI) 35.0–56.4] with a median follow-up of 3.2 years. On univariable analysis, histopathological tumor regression with $\geq 10\%$ residual tumor and ypN-site 2–3 were negatively associated with OS [$\geq 10\%$ residual tumor: hazard ratio (HR) 2.60; 95% CI 1.22–5.54; $P=0.014$; ypN2–3: HR 3.59; 95% CI 1.60–8.06; $P=0.002$]. On multivariable analysis, only ypN-site 2–3 was predictive of OS (HR 3.67; 95% CI 1.55–8.69; $P=0.003$), whereas histopathological tumor regression with $\geq 10\%$ residual tumor was not (HR 2.24; 95% CI 0.98–5.10; $P=0.055$).

Conclusions ypN-site may have greater impact on OS than histopathological tumor regression in patients who received NAC plus surgery for non-type 4 LAGC.

Keywords Locally advanced gastric cancer · Neoadjuvant chemotherapy · Posttherapy nodal status · Histopathological tumor regression · Overall survival

Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide [1], and the prognosis of locally advanced gastric cancer (LAGC) remains poor, with 5-year survival of approximately 20–30% achieved with surgery alone in Western countries [2, 3]. Because of this poor prognosis, perioperative chemotherapy is nowadays a standard for LAGC in the Western world [2–5]. The aim of perioperative therapy is to down-stage primary tumors to achieve a

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microscopically complete resection, and to eliminate radiologically occult micrometastases, which may result in recurrent metastatic disease. Despite these attempts, up to half of the patients who undergo surgery will subsequently relapse and die of their cancer. Identification of patients at higher risk for recurrence after perioperative treatment plus surgery and requiring additional therapy to prevent relapse remains challenging.

Histopathological regression (HPR) of the primary tumor after chemotherapy has been demonstrated as an independent prognostic factor, namely the gold standard for response evaluation, and patients with < 10% residual tumor are classified as responder most often [6–9]. However, of note, about 30% of patients with an obvious HPR still die due to recurrence [10, 11]. The value of HPR of the primary tumor as a prognostic factor has recently been re-estimated alongside other clinicopathological factors [12–14].

This exploratory study analyses independent prognostic factors, including clinical and histopathological factors, within a prospectively enrolled non-type 4 LAGC patient cohort treated with neoadjuvant chemotherapy (NAC) followed by curative surgical resection.

Patients and methods

Included studies

To date, the Stomach Cancer Study Group of Japan Clinical Oncology Group (JCOG) has conducted four phase II trials to evaluate NAC with irinotecan plus cisplatin (JCOG0001) [15] and S-1 plus cisplatin (JCOG0405) [16] for non-type 4 LAGC with extended lymph node metastases (para-aortic and/or bulky nodal metastases along the celiac, splenic, common hepatic, or proper hepatic arteries), and with S-1 alone (JCOG0002) [17] and S-1 plus cisplatin (JCOG0210) [18] for large type 3 and type 4 (linitis plastica) tumors. In this exploratory study, we used individual patient data of 85 out of a total of 213 patients enrolled in these four phase II trials, who underwent curative resection of non-type 4 LAGC after NAC with available surgical specimen, as shown in Fig. 1. All surgical procedures included total or distal gastrectomy with abdominal D2 or more extended lymphadenectomy. No patient received postoperative adjuvant chemotherapy or chemo-radiotherapy, and was lost to follow-up.

Pathological diagnosis

Representative blocks with primary tumor were chosen by local pathologists and were collected centrally. Pathological specimens were evaluated on serial hematoxylin–eosin-stained sections by two pathologists and graded

for histopathological response according to the Becker's tumor regression grading [7, 8]; complete regression with absence of histopathologic evidence of malignancy, subtotal regression with < 10% residual tumor tissue, partial tumor regression with 10 to < 50% residual tumor, and minimal or no tumor regression with $\geq$ 50% residual tumor.

Macroscopic type, pathological depth of tumor invasion (ypT) and lymph node metastasis (ypN) were classified according to the Japanese Classification of Gastric Carcinoma [19]. In particular, nodal status was evaluated by topographical category of positive nodes, namely by N-site system (ypN-site); regional lymph nodes (LNs) were classified into 3 Compartments depending on the location of primary tumor (Supplement). ypN-site 0: no LN metastasis, ypN-site 1: LN metastasis confined to Compartment 1, ypN-site 2: LN metastasis confined to Compartments 1 and 2, ypN-site 3: LN metastasis extended to Compartment 3. The histologic tumor type was in accordance with the Lauren's classification [20].

Statistical analysis

Quantitative values are expressed as median and range, and categorical values with absolute and relative frequencies (count and percent). Overall survival (OS) was defined as the time from patient registration to death from any cause, censored at the last follow-up day for surviving patients, assessed using the Kaplan–Meier method. The hazard ratio (HR) of various factors in OS was calculated by stratified Cox proportional hazard model including the study as a stratification factor in uni- and multivariable analyses. A P value of less than 0.05 was considered as statistically significant and all statistical tests were conducted two-sided. All statistical analyses were performed using SAS 9.2 or more (SAS Institute, Cary, NC).

Results

Patient characteristics

The patients had a median age of 62 years (range 33–75) and were predominantly male (76.5%). All patients had a performance status (PS) of 1 or less on the Eastern Cooperative Oncology Group (ECOG) scale. Pathologic characteristics of the resected tumors such as macroscopic type, histology, ypT, and ypN-site are listed in Table 1. In all, 5 patients (5.9%) had a pathological complete response and 21 patients (24.7%) had a major histopathological response with < 10% residual viable cells in the primary tumor, whereas the remainder showed minor or no response. In detail, 15 of 26 (58%) patients with HPR < 10% and 10 of 59 (17%) patients with HPR $\geq$ 10% had ypN-site 0–1 disease.

Fig. 1 Flow diagram of the study population

Survival

All patients were followed up for at least 3 years with the median follow-up period of 3.2 years. For all 85 patients, 5-year overall survival (OS) was 46.0% [95% confidence interval (CI) 35.0–56.4] with a median OS of 3.8 years (95% CI 2.4–5.5) (Fig. 2a). Median OS was not reached in patients with < 10% residual tumor ($n = 26$), whereas that

was 2.7 years (95% CI 1.4–4.5) for patients with $\geq 10\%$ residual tumor ($n = 59$) ($P = 0.0136$) (Fig. 2b). Pathological nodal status, ypN-site, significantly discriminated the patient prognosis as shown in Fig. 2c, and median OS was not reached in patients with ypN-site 0–1 ($n = 25$), whereas that was 2.6 years (95% CI 1.5–4.0) for patients with ypN-site 2–3 ($n = 60$) ($P = 0.0034$) (Fig. 2d).

Table 1 Patient characteristics ($n=85$)

	<i>n</i>	(%)
Age median (range)	62 years	(33–75)
< 65	56	(65.9)
65 ≤	29	(34.1)
Sex		
Male	65	(76.5)
Female	20	(23.5)
ECOG PS		
0	78	(91.8)
1	7	(8.2)
Macroscopic type		
0	3	(3.5)
1	1	(1.2)
2	23	(27.1)
3	55	(64.7)
5	3	(3.5)
Histology		
Intestinal type	44	(51.8)
Diffuse type	41	(48.2)
Pathological depth of tumor invasion		
ypT1 (m, sm)	10	(11.8)
ypT2 (mp, ss)	37	(43.5)
ypT3 (se)	28	(32.9)
ypT4 (si)	7	(8.2)
Missing	3	(3.5)
Pathological nodal status		
ypN-site 0	12	(14.1)
ypN-site 1	13	(15.3)
ypN-site 2	31	(36.5)
ypN-site 3	29	(34.1)
Residual viable cell		
0%	5	(5.9)
0% <, < 10%	21	(24.7)
10% ≤, < 50%	28	(32.9)
50% ≤	31	(36.5)

ECOG Eastern Cooperative Oncology Group, PS performance status

Prognostic factors

Various clinicopathological factors, such as sex, age, histology of the primary tumor, pathological nodal status (ypN-site), and graded histologic response of the primary tumor to NAC are analyzed as potential prognostic factors for OS in Table 2. On univariable analysis, histopathological tumor regression with $\geq 10\%$ residual tumor and ypN-site 2–3 were negatively associated with OS ($\geq 10\%$ residual tumor: HR 2.60; 95% CI 1.22–5.54; $P=0.014$; ypN-site 2–3: HR 3.59; 95% CI 1.60–8.06; $P=0.002$). On multivariable analysis, only ypN-site 2–3 was independently predictive of shorter OS (HR 3.67; 95% CI 1.55–8.69; $P=0.003$), whereas

histopathological tumor regression with $\geq 10\%$ residual tumor lost its prognostic relevance, though demonstrating statistically marginal associations with shorter OS (HR 2.24; 95% CI 0.98–5.10; $P=0.055$).

Discussion

This study demonstrates that in patients who received NAC followed by curative surgery for non-type 4 LAGC, the lymph node status in the resection specimen, ypN-site, but not the HPR of the tumor is the primary arbiter of OS.

Although the findings from the largest series of LAGC support HPR of the primary tumor as an independent prognostic factor [8], there are other studies that contradict this finding and thus support pathologic posttherapy nodal status as the only independent predictor of OS in LAGC patients treated with NAC plus surgery [12–14, 21]. Posttherapy nodal status seems to be superior to HPR in reflecting the extent of radiologically occult metastatic tumor load that is resistant to chemotherapy. In patients with node-positive disease after NAC plus surgery, switching to a non-cross resistant regimen other than NAC regimen may be appropriate as a postoperative chemotherapy.

In this study, nodal status was evaluated by topographical category, ypN-site [19], but not numerical category of metastatic lymph nodes, ypN-number [22, 23], since ypN-number system had not been employed in Japan during the period in which four JCOG phase II trials included in this study were conducted. With respect to the association between ypN-site status and ypN-number status, either nodal status showed similar survival probabilities in gastric cancer [24–26], or when having the same ypN-number status, ypN-site status became a strong predictor of survival in patients with adenocarcinoma of the gastroesophageal junction [27]. Although the recent literature has emphasized ypN-number status as a significant prognosticator in LAGC treated with NAC followed by surgery [12–14, 21], to the best of our knowledge, this is the first study to investigate the survival prediction by ypN-site status among patients who underwent NAC followed by surgical resection of LAGC.

Histopathological tumor regression lost its prognostic relevance, though demonstrating statistically marginal associations with OS in Table 2. It was previously shown that relevant percentage of patients with $< 10\%$ residual tumor following NAC showed persisting lymph-node metastases [11, 21], and one-third of patients classified as histopathological responders died due to recurrence, mostly occurring as distant metastases [10, 11]. In this cohort, certainly, patients with HPR $< 10\%$ had lymph-node metastases in 58% (15/26) versus 98% (58/59) with HPR $\geq 10\%$ (data not shown). These findings may be responsible for the marginal prognostic relevance of HPR in multivariable analysis.

Fig. 2 **a** Overall survival of all patients. **b** Overall survival of all patients stratified by histopathological regression with < 10% residual tumor versus with ≥ 10% residual tumor. **c** Overall survival of all

patients stratified by ypN-site (ypN-site 0 versus ypN-site 1 versus ypN-site 2 versus ypN-site 3). **d** Overall survival of all patients stratified by ypN-site 0,1 versus ypN-site 2,3

As shown in Fig. 1, 71 (83.5%) of the analyzed 85 patients had extended nodal disease, while the remainder had large type 3 but not type 4 tumors which were excluded because of the uncertainty of HPR as a prognostic factor for macroscopic type 4 tumors [28]. Of these 71 patients, 42 patients had clinically positive para-aortic LNs before NAC because ypN-site system employed in this study dealt the para-aortic nodes as regional ones classified ypN-site 3. This is a great contrast to the recent studies [12–14, 21] in which clinically positive para-aortic LNs were not eligible for NAC. On the other hand, the proportions of 30.6% for a complete or major HPR and 5.9% for a complete HPR in our study are in line with the published reports with

21–25% complete or subtotal regression and 4–7% complete regression for LAGC after preoperative chemotherapy [6, 8, 11, 12]. Furthermore, the 5-year OS of 69.2% (95% CI 47.8–83.3) observed in our patients with < 10% residual tumor is comparable to the outcomes seen in previous 2 studies with 57% [11] and 60% [10] including patients with a complete regression only. Our very similar anti-tumor effect and survival data may justify the generalizability of the results of this study.

Among 71 patients with extended nodal disease, 39 patients had disease relapse, 7 of 20 patients (35%) with < 10% residual tumor and 32 of 51 patients (63%) with ≥ 10% residual tumor, involving nodal recurrence in

Table 2 Prognostic factors for overall survival of all patients

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Male (vs. female)	0.84	0.41–1.69	0.616	0.57	0.27–1.22	0.147
Age						
65 ≤ (vs. < 65)	1.13	0.63–2.04	0.678	1.34	0.72–2.48	0.361
Histology						
Intestinal (vs. diffuse)	1.19	0.66–2.15	0.562	0.94	0.50–1.75	0.843
Nodal status						
ypN-site 2,3/(vs. ypN-site 0,1)	3.59	1.60–8.06	0.002	3.67	1.55–8.69	0.003
Viable cell						
10% ≤ (vs. < 10%)	2.60	1.22–5.54	0.014	2.24	0.98–5.10	0.055

HR hazard ratio, CI confidence interval

3 and 24 patients, respectively, peritoneal dissemination in 0 and 2 patients, and hematogenous recurrence in 4 and 12 patients.

The limitations of this study include the lack of prognostically relevant factors like postoperative complications [29, 30] or pretherapeutic nutritional status [31–33], and a small sample size which might have affected the marginal prognostic relevance of HPR. In addition, 15 patients without available surgical specimen were not included in this study, which might have led to the selection bias. In contrast, a strength of this study is the use of multi-institutional prospective data.

In conclusion, our study demonstrates that posttherapy topographical nodal status, ypN-site, predicts survival of patients who received NAC followed by curative surgical resection for non-type 4 LAGC with extended nodal metastases. This finding warrants further investigation to identify which post-therapeutic nodal status, ypN-site or ypN-number, would be a more suitable prognosticator for those patients as well as ordinary LAGC without extended nodal metastases.

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Compliance with ethical standards

Conflict of interest Dr. Fujitani reports personal fees from Taiho Pharmaceutical Co., Eli Lilly, Bristol-Myers Squibb, Ono Pharmaceutical Co. and Yakult Honsha Co. Ltd. outside the submitted work. Dr. Nakamura reports grants from Ministry of Health, Labour and Welfare, Japan, Japan Agency for Medical Research and Development (AMED) during the conduct of the study, and personal fees from Taiho Pharmaceutical Co., Chugai Pharmaceutical Co. and Bayer outside the submitted work. Mr. Mizusawa reports grants from Ministry of Health, Labour and Welfare, Japan, Japan Agency for Medical Research and Development (AMED) during the conduct of the study, and personal fees from Taiho Pharmaceutical Co. outside the submitted work. Dr. Kuwata reports grants from Ono Pharmaceutical Co. and Daiichi-Sankyo Pharmaceutical Co., and personal fees from AstraZeneca and MSD outside the submitted work. Dr. Katayama reports grants from Ministry of Health, Labour and Welfare, Japan, Japan Agency for Medical Research and Development (AMED) during the conduct of the study, and personal fees from Johnson & Johnson outside the submitted work. Dr. Yoshikawa reports personal fees from Ono Pharmaceutical Co., Bristol-Myers Squibb, MSD, Taiho Pharmaceutical Co., Chugai Pharmaceutical Co., Pfizer, Nihon Kayaku Pharmaceutical Co., Covidien, Johnson and Johnson, Olympus and Eli Lilly outside the submitted work. Dr. Boku reports grants from Taiho Pharmaceutical Co. and Ono Pharmaceutical Co., and personal fees from Taiho Pharmaceutical Co., Ono Pharmaceutical Co. and Bristol-Myers Squibb outside the submitted work. Dr. Terashima reports personal fees from Taiho Pharmaceutical Co., Chugai Pharmaceutical Co., Ono Pharmaceutical Co., Bristol-Myers Squibb, Yakult Honsha Co. Ltd., Takeda Pharmaceutical Co., Eli Lilly, Pfizer and Daiichi Sankyo Pharmaceutical Co. outside the submitted work. Dr. Fukuda reports grants from National Cancer Center and the Ministry of Health, Labour and Welfare of Japan during the conduct of the study, and personal fees from Taiho Pharmaceutical Co. and Chugai Pharmaceutical Co. outside the submitted work. Dr. Sano reports personal fees from Taiho Pharmaceutical Co., Chugai Pharmaceutical Co., Eli Lilly, Daiichi Sankyo Pharmaceutical Co. and Ono Pharmaceutical Co. outside the submitted work. Dr. Sasako reports personal fees from Taiho Pharmaceutical Co. during the conduct of the study, and personal fees from Chugai Pharmaceutical Co., Yakult Honsha Co. Ltd., Ono Pharmaceutical Co., Eli Lilly, Bristol-Myers Squibb and Sanofi Aventis outside

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Ethical statement/human rights statement All study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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